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# Introduction to the special topic "Stem cells and regenerative medicine"

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Stem cells are cells that can self-renew and differentiate. Conceptually, stem cells should be able to generate all functional cells that are required for cell therapy and tissue engineering. Although naturally existing stem cells can be harvested from different parts of the body through various developmental stages, the technical difficulties in obtaining, maintaining and differentiating stem cells hindered the progress of stem cell application in regenerative medicine. In 2006, Yamanaka et al. reported a groundbreaking finding that somatic cells (for example, fibroblasts) can be "artificially" induced to a pluripotent state by introduction of four transcription factors—Oct4, Sox2, c-Myc and Klf4, and the resultant cells were named induced pluripotent stem cells (iPSCs) [1]. In 2010, Wernig et al. found that fibroblasts can be directly converted to another kind of somatic cells—neurons, by using 3 factors—Ascl1, Brn2, and Myt1l, suggesting different lineages of cells can be switched given sufficient and necessary cues [2]. In agreement with this hypothesis, researchers have also successfully converted terminally differentiated somatic cells into adult tissue stem cells, such as neural stem cells. In light of such paradigm shift discoveries that stem cells can now be readily generated from somatic cells, both public and private funding agencies have poured a great deal of investment into this area of research, and recent years have seen remarkable advances in the basic science and the clinical applications of stem cells. In this special topic, we have included five articles that reviewed recent progress in stem cell biology and its applications in regenerative medicine.

In the article written by Xu DaWei and colleagues [3], the roles of the "stemness enzyme"–telomerase in stem cell biology were reviewed and discussed. Telomerase plays a central part in maintaining telomere length at the end of chromosomes. Most somatic cells lack telomerase activity and due to the end replication problem, telomeres are shortened with each round of cell division. Once the telomere length reaches a critical threshold, growth arrest or apoptosis will be triggered. Since one feature of stem cells is the ability to self-renew, telomerase is inevitably involved in the biology and phenotypes of stem cells. In this review, Xu et al. first summarized telomerase activity in normal and cancer cells. Telomerase reverse transcriptase (TERT) is the rate limiting component for telomerase activity and its expression is generally repressed in normal cells (except in stem cells) but is activated in up to 90% of human malignancies. Then the authors discussed the essential roles of telomerase in different types of stem cells—embryonic stem (ES) cells, adult stem cells, and iPS cells. In ES cells, TERT is highly expressed and telomerase activity is necessary for maintaining the immortal and pluripotent phenotypes of ES cells. Klf4, β-catenin (the effector of Wnt pathway), and HIF-1α have been found to interact with TERT as part of the regulatory mechanism. In adult stem cells, TERT expression is relatively lower than that in ES cells, and telomerase activity is not only required for stemness maintenance, but also necessary for the other aspects of stem cells,

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such as cell mobilization, mitochondria functions, and/or epigenetic status. During the reprogramming process to induce iPS cells, telomerase activity is activated and the level of activation may determine the extent of reprogramming, with the fully reprogrammed cells expressing the highest level of telomerase activity. In addition, the authors mentioned that controversy still exists with regard to whether iPSCs derived from patients carrying mutation of TERT, TERC or dyskerin can be used to model the progeria diseases. In the end, the authors discussed the functions of telomerase and alternative telomere-lengthening mechanism in cancer stem cells.

In addition to telomerase, other regulatory mechanisms also play critical roles in stem cell biology. Zhao Chen [4], in his article, discussed paracrine signaling activities in stem cell renewal and neoplastic tumor growth. The interaction between epithelial cells and stromal cells is key to embryonic development, adult tissue homeostasis and tumorigenesis. Hedgehog (Hh) is one of the major morphogens produced by epithelial cells and can exert effects in an autonomous manner on epithelial cells themselves, and in a non-autonomous manner on the stromal cells. In turn, stromal cells can respond to Hh signaling and secret soluble proteins that influence epithelial cells. Aberrant signaling in either the autonomous or the non-autonomous part can lead to tumor development. Hh may also directly affect stem cells, such as hematopoietic stem cells (HSCs) and the epithelial stem cells in bladder urothelium, although the percentages of cells expressing Hh or responding to Hh are not clear. Wnt is another family of morphogens that comprise 19 members. Wnt can be secreted by both the epithelial and stromal cells and the mainly responsive cells are epithelial stem cells. Proper Wnt signaling is critical for the maintenance of epithelial stem cells and dis-regulation is often associated with breast cancer. In some tissues, both Hh and Wnt pathways are active. The author continued to discuss how these two pathways negatively regulate each other in neural tube development and positively regulate each other in bladder urothelium. At last, Zhao revealed recent progress in drug development that target Hh and/or Wnt pathways to facilitate tissue regeneration or cancer treatment.

The crosstalk between major signaling pathways is complex. Wnt pathway not only interacts with Hh pathway, but also interacts with Notch pathway. An Songzhu, Li Ling-Song and colleagues [5] further discussed the intertwined network between Notch and Wnt signaling in their article. They first summarized the roles of Notch and Wnt pathways in normal cells separately, and then pointed out that these two pathways interact in different contexts. In hair follicle, β-catenin activates the gene encoding Jagges-1, a Notch ligand. In stem cell/progenitor cells, β-catenin can bind to the cytoplasmic tail of Notch which results in the degradation of β-catenin, suggesting a negative interaction between the two pathways. The authors then presented recent progress in drug development that target the two pathways individually or in combination, and illustrated how to take advantage of the crosstalk to target an otherwise "undruggable" pathway.

Stem cells are not only valuable resources for drug development, but also hold promise for regenerative medicine. Some types of adult stem cells have been successfully applied in clinics, for example, HSCs to treat leukemia. HSCs can give rise to all kinds of cells in blood, including red blood cells (RBCs), and may provide a solution to RBC shortage in developing countries including China. Pei XueTao and colleagues [6] reviewed recent advances in RBC generation in their article. They first summarized different protocols for RBC generation from HSCs, and also pointed out the limitation in using HSCs given their limited ability of self-renewal. The authors further discussed the advantages and obstacles in using ES cells and iPS cells for RBC production. In addition, they presented current methods for directing ES/iPS cells towards HSCs which include a recent attempt to increase HSC production by adding Notch ligand to the culture. In the end, the authors discussed the present methods to derive RBCs from ES/iPS cells and mentioned that full maturation and efficient enucleation of erythroid cells still remain an issue in the field.

Another type of adult stem cells that have been broadly used in clinics is mesenchymal stem cells (MSCs). MSCs reside in many tissues, such as bone marrow, adipose tissue, umbilical cord blood, dental pulp etc. In addition to the basic stem cell features–self-renewal and plasticity, MSCs also possess other characteristics, such as the capacity to modulate immune signaling, and to produce trophic factors. Considering the above beneficial features, MSCs have been successfully used in clinical trials to treat osteoarthritis (OA). Cao Wei and colleagues [7] reviewed the history and current state of MSC therapy for OA. MSCs are the resident cells in joint, and their aberrant activity is closely related to the onset of pathological changes in OA. MSCs can give rise to chondrocytes, adipocytes, and osteocytes; and chondrocytes are the major component of cartilage. In contrast to traditional therapies that resulted in poor clinical consequences without cartilage repair, intra-articular delivery of MSCs has demonstrated feasibility, safety and efficacy. After introducing the conventional therapies for OA treatment, the authors compared cell therapies using different sources—chondrocytes, adipose-derived MSCs, and bone marrow derived MSCs, with preclinical and clinical data. Finally, the authors illustrated potential mechanisms underlying the efficacy of MSCs, which may involve Wnt, BMP-2, Indian Hedgehog, and MAPK signaling pathways.

Stem cell based regenerative medicine is a very active field with great potentials. This collection of five review articles does not try to cover the width and depth of this dynamic field; rather, it is to highlight some selected progresses made from mechanistic studies of stem cell biology to clinical applications. It is intended to encourage more research interests to expand the current scope of regenerative medicine.

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5 An SM, Ding Q, Zhang J, Xie JY, Li LS. Targeting stem cell signaling pathways for drug discovery: advances in the Notch and Wnt pathways. Sci China Life Sci, 2014, 57: 575–580
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**Biographical Sketch**

Chen ZhiGuo, Ph.D., Professor, Cell Therapy Center, Xuanwu Hospital Capital Medical University. He obtained his bachelor's degree from Department of Biochemistry and Molecular Biology, Nankai University in 1999 and then continued to pursue the Ph.D. degree in Department of Neurotec, Karolinska Institute, Sweden, with the degree thesis focusing on Neuroscience. In 2004, he was recruited to Stanford University as a postdoctoral fellow and worked on stem cell biology, particularly on the regulation and application of neural stem cells. In 2010, Dr. Chen started to work at Cell Therapy Center, Xuanwu Hospital Capital Medical University and continued his research on stem cell biology and regenerative medicine. In the past years, he has made contributions that shed light on the mechanisms underlying the immunological regulation of neural stem cells, and the application of native and reprogrammed neural cells for Parkinson's disease therapy.

**Biographical Sketch**

Zhang Yu, Ph.D., Senior Director, AP Head of Early-to-Candidate Unit, SARD. He was selected to the Special Program for the Gifted Young at the University of Science and Technology of China, where he got his bachelor's degree. He obtained his Ph.D. from Northwestern University and continued his research at Stanford University. Prior to joining sanofi aventis in 2008, Alex had been a professor at Capital Medical University in Beijing and director of Cell Therapy Center at Xuanwu Hospital for eight years. Originally trained as a neuroscientist in the field of developmental neurobiology, Dr. Zhang's current research interest focuses on the understanding of basic biological properties of stem cells and developing nonhuman primate models for stem cell-based therapy of degenerative diseases. His research on using pancreatic progenitor cells in treating diabetes has demonstrated efficacy in monkey models and is pending for clinical trials in human patients.